The changing face of prostate cancer in British Columbia 1988-2000

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Objective: *To evaluate changes of prostate cancer incidence, referrals, stage, treatment and outcomes delivered in British Columbia since the 1980's.*
Materials and methods: *Examination of the BC Provincial Tumour Registry, BC Cancer Agency (BCCA) and BC Medical Services Plan databases.*
Results: *The number of incident cases increased linearly from 1980 through 1990. Between 1991 and 1995 a harvesting effect was seen due to unofficial PSA screening, balanced by a post-harvest effect between 1995 and 1998. Since 1999 the incidence has resumed the linear trend extrapolated from the 1980's. The age-standardised incidence rate has recently risen in younger (<65yrs) men. The incidence of metastatic cancer has dropped from 14% of cases referred to the BCCA in 1988 to 3.5% in 2000. A steady proportionate increase in T1 and T2 referrals has occurred since 1988. PSA levels at referral are lower (mean PSA 10 nmol/L in 2000 versus 15 nmol/L in 1990. Gleason scores are higher, likely reflecting changes of interpretation of pathological grade.*
The number of men receiving any curative therapy has increased from 43% in 1990 to 53% by 1999, and the proportion treated with surgery has increased from 30% in 1990 to 50% by 2000. Mortality rates have been falling since 1991, and BC has the lowest mortality rate in Canada.
Conclusions: *Predictions of incidence have been beset by unanticipated external factors, and have underestimated actual incidence. Stage migration towards better prognosis tumours occurring in younger men has led to the increased use of surgery and brachytherapy and decreased use of external radiation.*

Key Words: prostate neoplasms, data collection, registries, vital statistics, therapeutics

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Introduction

The last decade has been a time of marked change in prostate cancer incidence and of disease aggressiveness. In the United States, the SEER program of the National Cancer Institute has provided descriptive epidemiology of the incidence and types of prostate cancer from 1986[1] and the most recent publication describes trends up to 1995.[2] Similar trends are occurring in Canada, but

have not been so widely described. A report from Saskatchewan[3] detailed changes of incidence and mortality that occurred in that province for the period 1970 to 1997.

The present monograph describes Provincial changes in incidence, treatment and mortality including more recent data up to the end of 2000. In addition it describes the trends, referrals, and prognostic factor profiles (Prostate Specific Antigen, (PSA), Stage and Grade), of those patients referred to the BC Cancer Agency (BCCA), whose mandate is to manage cancer services (excluding surgery) to the whole population of BC. An appreciation of these changes will help with future treatment, research, and resource planning.

Methodology and data sources

The BC Cancer Registry contains information on all patients diagnosed with prostate cancer in BC since 1970. Data was extracted where the diagnosis was made between 1980 and 2000 (data obtained August 2001), for all men with adenocarcinoma (ICD-0 81403) and tumour site prostate (C61.9). Death information is incomplete for 2000, but is complete for earlier years. The registry links to the BC Vital Statistics Agency, which allowed the calculation of mortality rates. Age standardized rates are calculated from comparison with the 1991 Canadian population.

The BC Cancer Agency database (CAIS), which is linked to the Cancer Registry, contains pertinent stage and treatment information on all patients referred to the BCCA. It does not record surgical treatments where these were performed more than 3 months after the initial referral. No pathological grading information or PSA data is collected within this database.

Internal BCCA Genito-Urinary Site Group databases have been established since 1988, and record stage, grade, PSA and treatment information on patients referred and treated with curative intent with external beam radiation therapy (EBRT). Such databases cover the periods 1988-1992 and also from mid 1994 –2000. These databases were developed to investigate tumour outcomes, but are here used to extract information available at diagnosis. Where possible crosschecks between databases has allowed verification of data and updating of missing information. Data for patients from 1993 has been extrapolated from earlier years, by a linear projection model, to provide estimates for this year.

The Medical Services Plan of British Columbia has provided numbers of patients treated with radical prostatectomy (any approach) for the years 1988 to 2000. The data was prepared for each fiscal year, and calendar year equivalents have been estimated by pro-rating from adjoining fiscal year rates.

Results

Incidence

The age-standardised incidence rate of prostate cancer in BC in 2000 was 138x10-^{5}. This compares with a projected Canadian average of 116 x10-^{5}, according to the Canadian Cancer Society (CCS).[4]

The age-adjusted incidence of prostate cancer in BC rose steadily through the 1980's, with a marked increase occurring in those under the age of 65, commencing in 1990 Figure 1. The rise for most age groups peaked in 1993, fell back to 1990 levels, and then remained largely stable since. However for

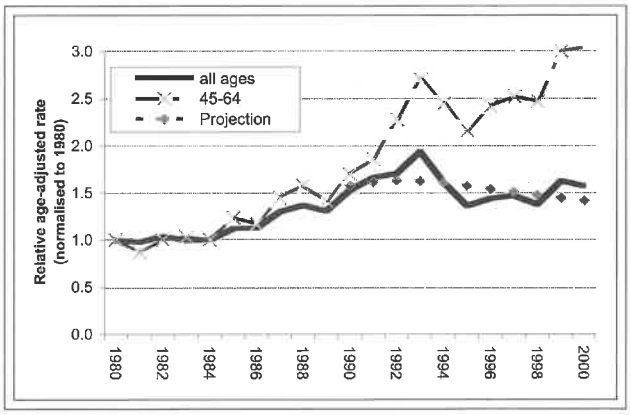

Figure 1a. Age-standardized incidence rates, 1980-2000. Normalized to 1980. Projections made in 1990 for the following decade are also shown.

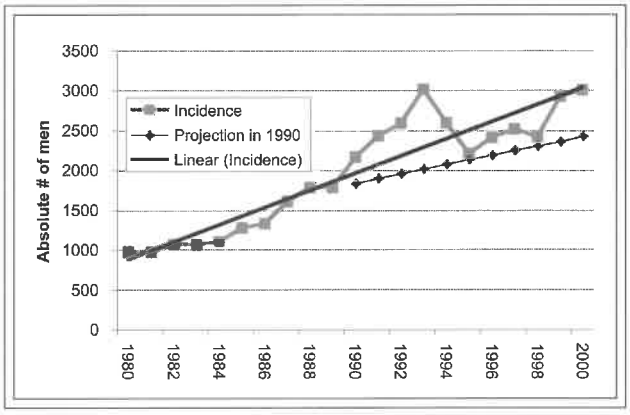

Figure 1b. Absolute numbers of men diagnosed with prostate cancer, 1980-2000. The trend line for the entire period and linear projections made in 1990 for the following decade are also shown.

young men aged under 65 there has been a second rise, recommencing in 1996, and the incidence doubled for this age-group between 1990 and 2000. As a result the mean age at diagnosis in BC has fallen from 72.9 years (median 73) in 1988 to 69.7 years (median 70) in 2000.

The proportion of incident cases referred to the BCCA within 1 year of diagnosis has fluctuated between 50% and 55%. Between 1991 and 1997 there were 1300 men who received radiation in Washington State, due to insufficient radiation therapy equipment availability in BC. Of these, 500 were referred to Washington State from the BCCA, and 800 were referred directly from urologists.

Treatment

The ratio of men receiving any 'curative' form of therapy (i.e. radical prostatectomy, external radiation or brachytherapy) has climbed from 43% in 1990 to 53% in 1999. The utilisation of each modality has also changed as new modalities such as brachytherapy have become available Figure 2.

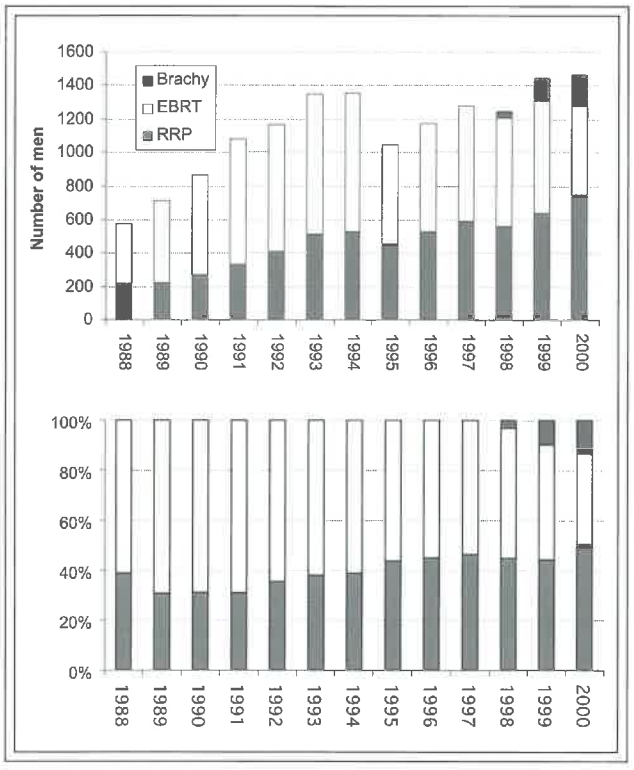

Figure 2. Use of 'curative' therapies, 1988-2000. Brachy = radioactive seed implantation (brachytherapy), EBRT = external beam radiation therapy, RRP = Radical retropubic or perineal prostatectomy. Year is the year of procedure. Upper: absolute numbers. Lower: as a proportion by year

The numbers of men receiving external radiation in 2000 is approximately the same as in 1990, whereas the number of men treated with radical prostatectomy has risen nearly threefold. The more recent introduction of brachytherapy in 1998 has only just begun to impact these numbers. In 2001 some 300 men are expected to undergo this form of treatment, compared with approximately 750 men having radical prostatectomy. About 10% of men treated annually with radical prostatectomy go on to receive adjuvant radiation therapy. This proportion has not changed during the time course of this study.

Prognostic factors

Stage information is only available on those patients referred to the BC Cancer Agency (50% of incidence). The proportion of referred patients with metastases at referral (N+ and/or M+) fell steadily from 122/885 cases (14%) in 1988 to only 56/1601 cases in 2000 (3.5%). This marked fall probably reflects the decreased incidence of metastatic disease, although a change of referral pattern is an additional possible explanation. In 1988 and in 1998 about 80% of those referred were referred within a year of diagnosis, but in the early 1990's that percentage fell to 60%, probably as a result of long waiting lists. There has been a steady increase in organ confined (T1-2) cancers, with T4 cancers becoming increasingly rare, and the numbers with T3 tumours also falling significantly Figure 3. Although it may be thought that the advent of brachytherapy has led to an increase referral rate of early stage cancers, the trend clearly antedates the introduction of brachytherapy in BC in 1998.

Other detailed patient information, such as Gleason score, PSA level and the use of androgen ablation is only available on those patients captured in internal GU Radiation databases, comprising 25% of all referred cases. There has been a gradual change of Gleason grade with time Figure 4. The change has been to increasingly assign higher Gleason scores. Where pathology review was undertaken, the change in Gleason recognition happened earlier than for those without pathology review. For example in 1994, 47% of cases were assigned Gleason 2-5, falling to 19% by 1997 and under 5% by 2000. For non-reviewed cases the falls were from 40% to 35% in 1997 to 19% in 2000.

PSA levels at referral, of patients subsequently treated with curative radiation have fallen from a mean of 15 ng/ml in 1990 to 10 ng/ml by 2000, and the proportion with PSA's <20 ng/ml has risen from

80% to 93% over the same time interval. These changes likely reflect patient selection for curative therapy as well as the presentation of patients with earlier disease as a result of PSA screening.

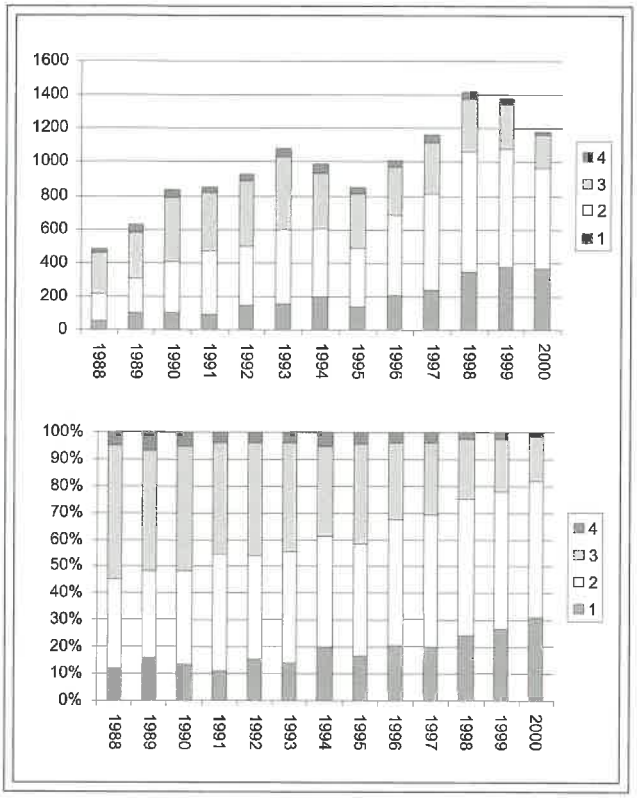

Figure 3. Clinical T Stage of referred patients. (1987 TNM system until 1993, 1992 TNM system since). Staging information is available on 91% of referred cases (50% of total incident cases). Upper: absolute numbers. Lower: as a proportion by year.

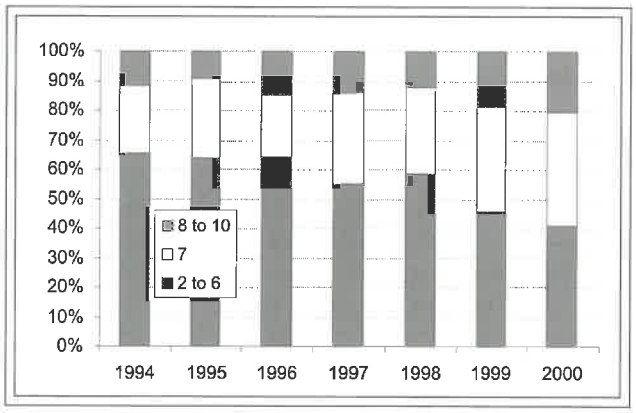

Figure 4. Gleason score changes by year of diagnosis, (patients referred to the BCCA, treated with curative intent only).

Mortality

The age-standardized mortality rates peaked in 1991 and declined by 15% from this level by 1999. The reduction in mortality has been slightly greater in the younger age group, falling by 19% over the same time period Figure 5. The age-standardised mortality-rate in BC is now 23x10-[5].

Discussion

The dramatic increase in incidence that occurred from about 1990 to 1993 is probably the result of increased utilisation of PSA screening. Similar changes have been described in Saskatchewan[3] where a sharp rise in incidence coincided with increased utilisation of PSA testing. In the United States a similar correlation between PSA testing and incidence has also been described.[5]

Although no PSA screening program had been sanctioned in Canada or in BC, a telephone survey conducted in January 1995 on a representative sample of Canadian men showed that 13% of men aged 50-59 and 24% of those aged 60 or more had had a PSA test.[6] A recent survey in Ontario identified PSA screening as the commonest reason for a PSA request, in those without an established diagnosis of cancer.[7]

In BC there was a flattening off of the age-adjusted incidence rates following this PSA harvest for older men, but in the last 2 years there has been a renewed increase in the age-adjusted (and therefore absolute numbers) of younger men (defined as 65 years or less) being diagnosed. PSA screening rates are not available in BC. However publicity and thus increased awareness and conduct of PSA testing in the community may be occurring. This phenomenon has not been described by previous Canadian reports.[3,8]

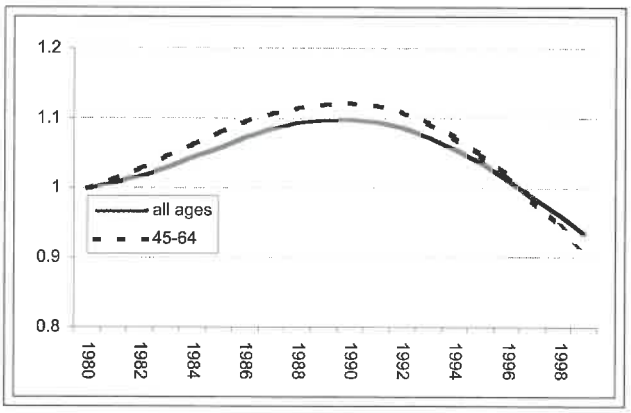

Figure 5. Age standardized mortality rates, normalized to 1980.

The most recent Cancer projections made by the National Cancer Institute of Canada for BC predict patient numbers for 2001 which are 10% less than the observed 2000 numbers, which itself were under-predicted by the preceding year's report.[4,9] The BCCA's predictions have likewise consistently under-predicted incidence, which is perhaps unsurprising given the volatility of the actual numbers.

The impact of the unanticipated rise that occurred in the early 1990's was vast. Waiting lists developed for radiation services and as an emergency measure, patients were sent out of Canada for treatment. Inability to plan for this surge, and insufficient time to develop increased capacity, rather than unwillingness to fund expansion delayed a solution until the latter 1990's. In 1995, and in 1998 new treatment facilities had been opened and by 2001, when the Vancouver Island cancer clinic had been rebuilt with increased radiation treatment machines, radiation waiting lists were within national standards (2 weeks from the decision to treat to the start of treatment) for the majority of patients. In addition, the numbers of men being treated with EBRT for prostate cancer had fallen from a peak of 840/year in 1993 to 550 by 2000. The experience of the last decade has shown the impact a new medical intervention (PSA screening), can lead to serious effects on health care delivery; particularly within a managed-care process.

The proportion of men receiving any 'curative' form of therapy (i.e. radical prostatectomy, external radiation or brachytherapy) has climbed from 43% in 1990 to 53% 10 years later. Similar findings have been reported in the US, where SEER data[1] shows that since 1987 the percentage of men receiving curative treatment has increased from 55% to 70% by 1995. Although the proportionate utilization of radical prostatectomy versus external radiation has increased in BC, this appears to be due to the use of RRP in those younger men with earlier stage cancer, who account for most of the recent increase. External radiation is being delivered to men with similar age and risk factors as previously, but as the numbers of men (both as a proportion of incident cases and also absolute numbers) with intermediate and high-risk prostate cancer are falling, so the use of EBRT has declined from a peak in 1993.

As we only have stage, PSA and Gleason score available for a proportion of referred cases, the changes we describe may not be applicable to the whole Provincial population. However, stage changes seen by us are similar to those reported in other countries, although no comparative data are available from other Canadian provinces. For example, in the United States the incidence of metastatic prostate cancer has been falling since the mid-1980's, and by 1996 had fallen to approximately 43% of 1990 levels.[10] Figures from BC are similar, with a decline in metastatic cancer at diagnosis from 14% to 3.5% over a 12 year time period.

T stage changes observed in referred patients have also been dramatic, with reductions in non-organ confined cancer (T3 or greater) from 50% of all non-metastatic referred cases in 1988 to 20% in 2000. Although some of this reduction may be related to the development of brachytherapy as a treatment option for prostate cancer, which in BC necessitates a referral to the BCCA, the stage shift antedates the development of this technique. In addition the stage shift preceded the introduction of PSA screening in BC, although continued stage shift since the early 1990's probably results from screening. Additional, unidentified factors may have contributed to the increased incidence that preceded PSA testing,[8] and therefore might also be associated with a subsequent decrease, as the same unidentified risk factors are removed from the population. Detailed stage information, such as T stage, is not generally available in the literature for comparison with other provinces or countries, but where broad stage information is provided, advanced cancers have also declined. In the future locally advanced prostate cancer will become increasingly rare, and this will impact on or ability to recruit for studies of such patients, and may also make the results of ongoing studies less applicable when mature results are available in another decade.

The change in the Gleason grade with time that we have observed is probably due to increased understanding of Gleason pattern recognition, rather than a true increase of tumour aggressiveness, as these changes occurred earlier in those men who had centrally-reviewed pathology, further suggesting that the change is not a result of a real change in pathological aggressiveness. A further possible explanation is a change in referral patterns, with proportionately more patients with lower Gleason scores undergoing surgery.

It is very tempting to ascribe the decreased mortality rates that others and we have observed as being due to PSA screening. However, when the biology of prostate cancer is considered, and data from other jurisdictions is also included, this is an unlikely scenario for several reasons. Firstly, PSA has the potential to detect a cancer about 5 1/2 years

earlier than it would have been detected clinically,[11] and even with failure of subsequent localized treatment, such as RRP or EBRT, it is unlikely that metastatic disease would develop for another 4-6 years. The use of hormone therapy would be expected on average to work for about 2-3 years, giving a minimum likely time from PSA-based diagnosis to death of 10-15 years.[12] In a report from the Princess Margaret Hospital,[13] the median time to use of hormones in those with Gleason 7 cancer, who failed external radiation therapy was 4.8 years, and then the time to death was 4.5 years from institution of hormone therapy. Prostate detection rates in different US states have not been shown to translate into death rate reductions in those states with increased PSA screening, diagnosis or treatment compared with those states with decreased detection, although these data do not exclude a possible future benefit with much longer follow-up.[14] In addition international trends in mortality show variations that are not explicable on the basis of uptake of PSA screening.[15] Mortality rates in the United States and Canada have been falling since 1991; earlier in some other countries (e.g. Italy, 1988) and some later (e.g. Germany, 1995). Such changes more likely result from changes of therapeutic intervention, as there have been consistent falls across all age-bands, which argue against changes in exposure to an environmental risk factor, which would more commonly be expressed as a cohort effect.[15] Alternative explanations are that the trends are an artefact due to changes in death certification, or result from increases in competing causes of death. Meyer[16] also suggests that decreases in Canadian mortality up to 1997 result from better prostate cancer management or improved treatment modalities. BC has the lowest mortality rates in the country, followed closely by Quebec.[9]

Changing therapies over the last decade, particularly the increased use of radical prostatectomy have occurred in BC. Brachytherapy was introduced in 1998, and in 2001 some 300 men will be treated with this technique compared with approximately 750 men with RRP. Whether one modality is 'better' than the other is uncertain. Published outcomes by modality[17] tend to favour RRP over EBRT, but these patients tend to have lower stage, grade and PSA tumours. Results achieved with brachytherapy appear to be at least as good as surgery[18] Nomograms[18-20] more accurately reflect the success of each modality than risk stratification systems[20] or physician experience or guesswork.[21] In addition more men with prostate cancer have concerns about quality of life, and the toxicities of modality vary considerably.[22,23]

In conclusion, the changes seen in BC over the last decade are similar to those reported from the United States, with increased prostate cancer incidence resulting from PSA testing in the early 1990's. A more recent 'second-wave' PSA-harvest may be occurring in younger men. Stage at diagnosis has reduced both for metastatic and non-metastatic cases, and more patients are being aggressively treated by means of RRP and brachytherapy. Mortality rates have been falling since 1991; the cause of which remains uncertain because of the long natural history of prostate cancer. □

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